REMARKS

Applicants have amended claims 1 to 8 to more clearly point out their invention. These amendments are not the addition of new matter. Regarding the units "µg/kg", these were inadvertently presented as "g/kg" in response to the Restriction Requirement.

Accordingly, Applicants respectfully ask that the Examiner enter the amendments.

Applicants respectfully traverse the rejection of claims 1 – 8 are rejected under 35 U.S.C. 112, first paragraph.

The Examiner states that the specification, is enabling for a method of inducing a permanent change in the neurological development of a rat, comprising treating a rat during the second post natal week with specified doses. The Examiner also states that the specification does not reasonably provide enablement for a method of treating any rodent during the second post natal week with any doses of any kainate receptor agonist.

To address the Examiner's objection to the term "treatment" recited in claim 1, Applicants have clarified the treatment method by replacing the phrase "treatment of a rodent" with the phrase "injecting said rat".

Further, amendments have been made to claim 1 to address the requirement that the kainate agonist an the dosage be defined in the claim. In

particular, Applicants have further defined the term "kainate receptor agonist" as a "systematically bioavailable kainate receptor agonist". In this respect, please note that there are two main categories of kainate receptor activators, one being the naturally occurring compounds including domoic acid, kainic acid, isodomoic acids, derivatives of kainic acid, etc., all of which are chemically similar and which are thought to act on brian kainate receptors following systemic administration, and the second being predominantly synthetic molecules that activate kainate receptors only in *in vitro* systems. Accordingly, the demonstrated utility of two compounds in the first category, i.e., kainate and domoate, in subconvulsive doses, is sufficient to support the predicted utility of the "systemically bioavailable" kainate receptor agonists. This approach in responding to the objection to the alleged broadness of the term "kainate receptor agonist" overcomes the objection.

The amended claims also define the dosage of the kainate receptor agonist in claim 1 as "subconvulsive", and delete the allegedly relative and indefinite term "low". The term "low" was originally used in the application, based on the knowledge of those skilled in the field, for dosages of kainate receptor agonists known to be below the threshold for inducing toxicity in rats, e.g. convulsions. Confulsions usually occur in neonatal rats upon treatment with doses of domoic acid above 50 µg/kg, and with doses of kainic acid at or above about 150 µg/kg. Figure 1 of the application shows that treatment with both 5 and 20 µg/kg doses of

domoic acid results in the desired syndrome in male rats. Figure 2 further illustrates that both 5 and 20 µg/kg domoic acid produces the desired syndrome in female rats. Positive testing results for 25 µg/kg and 100 µg/kg kainic acid are also provided for male and female rats in Example 3. The dosages used are all below the confulsive threshold, and thus, by defining the upper dosage in amended claim 1 as "subconvulsive", the amended claim 1, which has also been amended to recite a minimum does of "about 5 µg/kg", specifies a dosage range which would be reasonably predicted by one skilled in the art to have utility based on the factual evidence provided in the application. Based on the above, claims 5 to 8 are also believed to be supported by the application as filed, and thus not overly broad.

Claim 8 has been amended to specify 25 to 100 µg/kg kainic acid, rather than 20 to 50 µg/kg kainic acid as previously claimed.

Accordingly, Applicants respectfully ask that the Examiner withdraw the rejection under 35 U.S.C. §112, first paragraph.

Applicants also respectfully traverse the rejection of claims 1 – 8 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to the objection that the frequency and duration of dosing and

the age at which animals receive treatment were not sufficiently defined in claim 1, please note that it is clearly defined in amended claim 1 that the animals are administered repeated subconvulsive doses of the drug during the second postnatal week. The second postnatal week is a well-defined period of rat development, and one skilled in the art would be able to modify the frequency of the dosing during this period without undue experimentation.

The dosage units are all "µg/kg". The response to the Restriction Requirement inadvertently presented this unit as "g/kg". The amended claims recite all units in "µg/kg". Additionally, there is only one form of domoic acid ($C_{15}H_{21}NO_8$; molecular weight 311.33). However, the Sigma and Fluka catalogs have slightly different illustrations of the same chemical structure. In addition, different methods are used to isolate and purify the domoic acid from the biological source, and so they are listed separately.

To address the objection to the term "reproducible" in claim 1, Applicants have deleted the word from the claim.

To address the objection to the expression "mild to moderate stressor", enclosed please find two scientific papers which use the terms "mild" and "moderate" stress. These papers serve to establish that the allegedly contravening expression is actually well known and used in the art, and is therefore not indefinite. In particular, the paper by Akirav et al. (2004), refers in the abstract and

introduction to the use of cold (19°C) water in the water maze test as a moderate stress situation, and the use of warm (25°C) water in the water maze test as a mild stressor. The temperature of the water in the Morris Water Maze used in the present application, as mentioned on page 13 of the description, was 21°C. The second paper, by van den Buuse et al. (2002), refers to the open field test situation as a "mild stress" on page 208, lines 3 to 8.

Accordingly, Applicants respectfully ask that the Examiner withdraw this rejection under 35 U.S.C. §112 first paragraph.

Applicants respectfully traverse the rejection of claims 1 – 8 under 35 U.S.C. §112, second paragraph.

Regarding the term "permanent" recited in claim 1, please note that the inventors have found that the neurological changes are "permanent". In this regard, two recent publications from the inventors' laboratory that have been peer-reviewed by persons knowledgeable in the field, and which both contain the term "permanent" in the title; namely Doucette et al. Neurotoxicity Research 6:555-563, 2004 (Low doses of domoic acid during postnatal development produce permanent changes in rat behaviour and hippocampal morphology) and Bernard et al. Epilepsia 45 (suppl 7) pg. 40:1.076, 2004 (Permanent histological and behavioural changes produced by neonatal kainate receptor stimulation:). These papers are being submitted by a Supplemental Information Disclosure Statement.

The Examiner argues that these are relative terms and the use of these words depend upon the application used by the artisan.

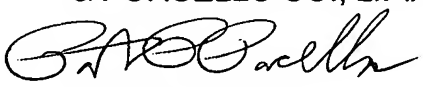
Applicants respectfully submit that their specification clearly define these terms especially in view of the above remarks and amendments to the claims.

Accordingly, Applicants respectfully ask that the Examiner withdraw the rejection under 35 U.S.C. §112, second paragraph.

Therefore, Applicants respectfully submit that claims 1 – 8, as amended, are in condition for allowance and respectfully ask that the Examiner pass the claims to issue.

Respectfully submitted,

EMCH, SCHAFFER, SCHAUB
& PORCELLO CO., L.P.A.



Patrick P. Pacella
Reg. No.: 25,463

P.O. Box 916
Toledo, Ohio 43697
Ph: (419) 243-1294
Fax (419) 243-8502